

ORIGINAL INVESTIGATIONS

Oral Anticoagulation, Aspirin, or No Therapy in Patients With Nonvalvular AF With 0 or 1 Stroke Risk Factor Based on the CHA₂DS₂-VASc Score



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ABSTRACT

BACKGROUND Even a single additional stroke risk factor in patients with atrial fibrillation may confer a risk of stroke. However, there is no consensus on how best to treat these patients.

OBJECTIVES Our objective was to investigate the risk of stroke and bleeding and the impact of antithrombotic therapy among low-risk patients, i.e., with 0 or 1 CHA₂DS₂-VASc (congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke/transient ischemic attack, vascular disease, age 65 to 74 years, sex category) score risk factor.

METHODS The nationwide cohort for this study was established by linking data from the Danish Civil Registration System, the Danish National Patient Register, and the Danish National Prescription Registry. We studied 39,400 patients discharged with incident nonvalvular atrial fibrillation with 0 or 1 CHA₂DS₂-VASc risk factor; 23,572 were not treated, 5,353 were initiated on aspirin, and 10,475 were initiated on warfarin.

RESULTS Stroke event rates for untreated low-risk patients (CHA₂DS₂-VASc = 0 [male], 1 [female]) were 0.49 per 100 person-years at 1 year and 0.47 per 100 person-years at full follow-up (intention-to-treat). Bleeding event rates among untreated low-risk patients were 1.08 per 100 person-years at 1 year and 0.97 at full follow-up. The presence of 1 additional stroke risk factor (CHA₂DS₂-VASc = 1 [male], = 2 [female]) among untreated patients increased the stroke rate at 1 year to 1.55 per 100 person-years, representing a significant 3.01-fold increase. At the 1-year follow-up, bleeding increased 2.35-fold, and death increased 3.12-fold.

CONCLUSIONS Low-risk patients (CHA₂DS₂-VASc = 0 [male], 1 [female]) have a truly low risk for stroke and bleeding. With 1 additional stroke risk factor (CHA₂DS₂-VASc = 1 [male], = 2 [female]), there was a significant increase in event rates (particularly mortality) if nonanticoagulated. (J Am Coll Cardiol 2015;65:1385-94) © 2015 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

CT = continuous treatment

ESC = European Society
of Cardiology

HR = hazard ratio

ICD-10 = International
Classification of Diseases,
10th Revision

ITT = intention-to-treat

NCB = net clinical benefit

NICE = National Institute for
Health and Care Excellence

NOAC = non-vitamin K
antagonist oral anticoagulant

VKA = vitamin K antagonist

Atrial fibrillation (AF) confers a risk of strokes, which is associated with high mortality and disability. The risk of stroke is reduced by oral anticoagulation therapy, which, in historical trials using vitamin K antagonists (VKAs) such as warfarin, significantly reduced stroke/systemic embolism by 64% and all-cause mortality by 26% (1). The effect size of VKA is probably underestimated because many strokes in VKA-treated patients occurred while off therapy or during subtherapeutic anticoagulation. In contrast, aspirin reduces stroke by a nonsignificant 19%, with no impact on mortality (1).

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Although AF increases stroke risk 5-fold, this risk is not homogeneous and depends on additional stroke risk factors (2,3). In addition, the landscape for stroke prevention in AF has changed with the recognition of the need for well-managed VKA (with average time-in-therapeutic-range >65% to 70%) (4,5) and the recent availability of the non-vitamin K antagonist oral anticoagulants (NOACs [previously referred to as new or novel oral anticoagulants (6)]), which offer relative efficacy, safety, and convenience compared with the VKAs (7).

Guidelines have evolved to account for these developments. The 2012 Focused Update of the European Society of Cardiology (ESC) guidelines recommend a clinical practice shift, such that the initial decision step is to identify low-risk patients (age <65 years and lone AF [irrespective of sex]; i.e., a CHA₂DS₂-VASc [congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischemic attack, vascular disease, age 65 to 74 years, sex category] score of 0 for male patients, 1 for female patients) who do not need any antithrombotic therapy (7). Patients with ≥1 additional stroke risk factor can subsequently be offered stroke prevention with oral anticoagulation. The 2014 National Institute for Health and Care Excellence (NICE) guidelines recommend a similar approach, and aspirin is not recommended (8). However, the 2014 American Heart Association/American College of

Cardiology/Heart Rhythm Society guidelines recommend oral anticoagulation for patients with a CHA₂DS₂-VASc score ≥2 and no therapy for those with a CHA₂DS₂-VASc score of 0; for patients with a CHA₂DS₂-VASc score of 1, no therapy, aspirin, or oral anticoagulation is recommended (9).

Given that even a single risk factor in patients with CHA₂DS₂-VASc scores of 1 may confer a high risk of stroke, as evident in a recent analysis (10), our principal objective was to investigate the impact of anticoagulation in patients with CHA₂DS₂-VASc scores of 0 to 1, particularly focusing on risk factors for stroke and bleeding among low-risk patients (CHA₂DS₂-VASc = 0 [male], 1 [female]) and those with 1 additional stroke risk factor (CHA₂DS₂-VASc = 1 [male], = 2 [female]).

METHODS

REGISTRY DATA. The nationwide cohort for this study was established by linking data from the Danish Civil Registration System, the Danish National Patient Register, and the Danish National Prescription Registry by using the unique personal registration number provided to all Danish citizens. The Danish National Patient Register has maintained extensive data on >99% of all hospital admissions in Denmark since 1977. The data include date of admission and discharge diagnosis and have been coded according to the International Classification of Diseases, 10th Revision (ICD-10), since 1994. The Danish National Prescription Registry contains date of purchase, package size, and type of drugs coded according to the international Anatomical Therapeutic Chemical Classification System for all subsidized prescriptions since 1995.

STUDY POPULATION. We identified all patients with an incident hospital diagnosis of nonvalvular AF in the study period (from 1998 to the end of June 2012) (Figure 1). Patients immigrating within 2 years were excluded. Nonvalvular AF was defined as the presence of AF (ICD-10 code I48) and baseline absence of mitral stenosis or mechanical heart valves (ICD-10 codes I05 or Z952 through Z954). The index date was defined as 14 days after hospital discharge for hospitalized patients and 14 days after diagnosis for ambulatory patients. The study start of 1998

has been on the Speakers Bureau for Bayer, Bristol-Myers Squibb/Pfizer, Roche Diagnostics, Boehringer Ingelheim, and Takeda Pharma. Dr. Rasmussen has been on the Speakers Bureau for Bayer, Bristol-Myers Squibb/Pfizer, Roche Diagnostics, Boehringer Ingelheim, and Takeda Pharma. Dr. Skjøth has reported that he has no relationships relevant to the contents of this paper to disclose.

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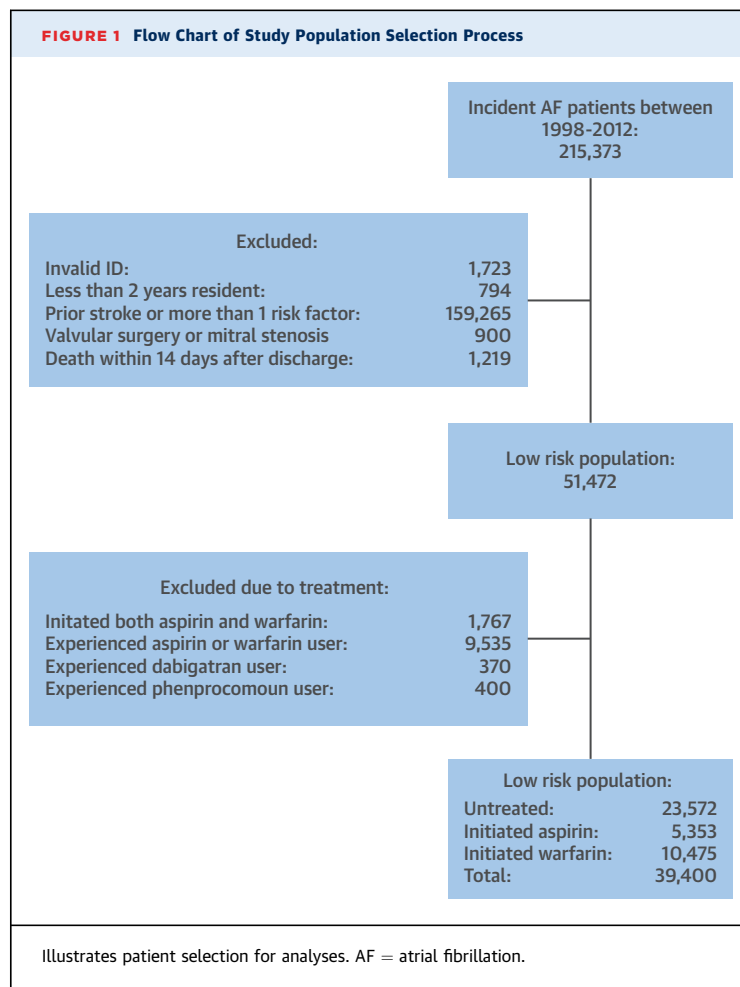
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entailed establishing a baseline status of comorbidities on the basis of hospital diagnoses and claimed prescriptions for a period before 1998. For comorbidities, a prescription within 1 year before the index date was required to assume that a patient was in treatment. To establish a low-risk patient population, male patients with CHA₂DS₂-VASC scores >1 and female patients with CHA₂DS₂-VASC scores >2 were excluded. Patients not treated with warfarin, phenprocoumon, aspirin, and dabigatran etexilate within 1 year before the index date were allocated to the not-treated group. Patients with a prescription of warfarin or aspirin within 4 months before the index date were allocated to the treated group. Patients initiated on NOACs, phenprocoumon, or with additional warfarin or aspirin prescriptions between 4 months and 1 year before the index date were excluded. This established a new-users design, which has been recommended for evaluating medication effects with an additional focus on newly diagnosed patients (11).

OUTCOMES AND COMORBIDITY. The outcome of stroke/thromboembolism was defined as a combined endpoint of ischemic stroke (ICD-10 codes I63 and I64) and systemic embolism (ICD-10 code G45). Bleeding comprised the following events: intracranial hemorrhage (ICD-10 codes I60 and I61); major bleeding (ICD-10 codes D62, J942, H113, H356, H431, N02, N95, R04, R31, and R58); gastrointestinal bleeding (ICD-10 codes K250, K260, K270, K280, and K290); and traumatic intracranial bleeding (ICD-10 codes S063C, S064, S065, and S066). Both primary and secondary diagnoses were included. Supplementary analyses regarding the outcomes of stroke/thromboembolism (primary diagnoses only), ischemic stroke, and intracranial hemorrhage were performed. The outcome of all-cause death was extracted from the Danish Civil Registration System. Diagnoses and medications to establish comorbidity, as summarized in the CHA₂DS₂-VASC score and the HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly [>65 years], drugs/alcohol concomitantly) score, are presented in [Online Tables 1 and 2](#).

STATISTICAL METHODS. The effects of treatment strategy were analyzed as intention-to-treat (ITT) and supplemented by a continuous treatment (CT) analysis. CT was assumed to be interrupted by prescription of an anticoagulant other than the initial type or if initiating treatment.

Event rates of reported endpoints were calculated as the number of events per 100 person-years. Person-time was censored at the first occurring event:



electrical cardioversion; AF ablation; death; emigration; end of study (December 31, 2013); or treatment interruption (CT analysis only). Effect of 1 risk factor on outcome within treatment group (no treatment, aspirin initiated, or warfarin initiated) and contrasts between treatments within risk factor strata (no risk factors or 1 risk factor) were estimated by using Cox proportional hazards models. They were reported as crude effects and adjusted for potential confounders (sex; inclusion year [categorical]; abnormal renal function; abnormal hepatic function; angiotensin receptor blockers or angiotensin-converting enzyme inhibitor, beta-blocker, or nonsteroidal anti-inflammatory drug treatment; previous electrical cardioversion or ablation).

Sensitivity analyses regarding the choice of index date were performed by assuming index date at date of diagnosis and 30 days after hospital discharge (results not shown). Data were analyzed by using Stata/MP version 13 (Stata Corporation, College Station, Texas). A p value <0.05 was considered statistically significant.

TABLE 1 Characteristics of Patients at Baseline and Day 14 After Discharge With Incident AF Diagnosis							
	No Treatment		Aspirin Initiated		Warfarin Initiated		All
	No Risk Factors	1 Risk Factor	No Risk Factors	1 Risk Factor	No Risk Factors	1 Risk Factor	
No. of patients	14,115	9,457	2,182	3,171	4,072	6,403	39,400
AF as primary diagnosis	11,499 (81.5)	6,125 (64.8)	1,790 (82.0)	2,277 (71.8)	3,456 (84.9)	5,113 (79.9)	30,260 (76.8)
Female	5,440 (38.5)	4,422 (46.8)	774 (35.5)	1,256 (39.6)	854 (21.0)	2,134 (33.3)	14,880 (37.8)
Age at AF, yrs	52 (42–59)	66 (59–70)	57 (51–61)	65 (59–70)	57 (50–61)	65 (59–70)	59 (51–65)
CHA ₂ DS ₂ -VASc score	0.39 ± 0.49	1.47 ± 0.50	0.35 ± 0.48	1.40 ± 0.49	0.21 ± 0.41	1.33 ± 0.47	0.86 ± 0.72
CHF or LVD	0	333 (3.5)	0	73 (2.3)	0	322 (5.0)	728 (1.8)
Hypertension	0	3,044 (32.2)	0	1,240 (39.1)	0	2,516 (39.3)	6,800 (17.3)
Age >65 yrs	0	5,265 (55.7)	0	1,527 (48.2)	0	3,279 (51.2)	10,071 (25.6)
Diabetes	0	483 (5.1)	0	90 (2.8)	0	182 (2.8)	755 (1.9)
Myocardial infarction	0	201 (2.1)	0	206 (6.5)	0	62 (1.0)	469 (1.2)
Peripheral arterial disease	0	139 (1.5)	0	40 (1.3)	0	44 (0.7)	223 (0.6)
HAS-BLED	0.38 ± 0.60	1.42 ± 0.76	1.13 ± 0.38	2.05 ± 0.53	0.32 ± 0.52	1.31 ± 0.66	0.95 ± 0.85
Bleeding	825 (5.8)	1,100 (11.6)	136 (6.2)	291 (9.2)	179 (4.4)	497 (7.8)	3,028 (7.7)
Abnormal renal function	215 (1.5)	406 (4.3)	15 (0.7)	45 (1.4)	28 (0.7)	94 (1.5)	803 (2.0)
Abnormal hepatic function	85 (0.6)	110 (1.2)	11 (0.5)	7 (0.2)	1 (0.0)	10 (0.2)	224 (0.6)
Clopidogrel	24 (0.2)	53 (0.6)	20 (0.9)	140 (4.4)	7 (0.2)	13 (0.2)	257 (0.7)
ARB or ACE inhibitor	280 (2.0)	1,997 (21.1)	54 (2.5)	832 (26.2)	100 (2.5)	1,866 (29.1)	5,129 (13.0)
Beta-blocker	4,010 (28.4)	3,801 (40.2)	1,454 (66.6)	2,137 (67.4)	2,336 (57.4)	3,995 (62.4)	17,733 (45.0)
NSAID	3,311 (23.5)	2,700 (28.6)	577 (26.4)	913 (28.8)	971 (23.8)	1,710 (26.7)	10,182 (25.8)
Years follow-up, ITT	6.75 ± 4.46	5.81 ± 4.36	5.83 ± 3.96	5.72 ± 3.96	4.79 ± 4.67	5.01 ± 4.42	5.91 ± 4.45
Years follow-up, CT	4.94 ± 4.30	2.92 ± 3.36	4.76 ± 3.78	4.17 ± 3.74	3.47 ± 4.12	3.55 ± 3.89	4.01 ± 4.02

Values are n (%), median (interquartile range), or mean ± SD.
ACE = angiotensin-converting enzyme; AF = atrial fibrillation; ARB = angiotensin receptor blocker; CHA₂DS₂-VASc = congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischemic attack, vascular disease, age 65 to 74 years, sex category; CHF = congestive heart failure; CT = continuous treatment; HAS-BLED = hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly (>65 years), drugs/alcohol concomitantly; ITT = intention-to-treat; LVD = left ventricular dysfunction; NSAID = nonsteroidal anti-inflammatory drugs.

RESULTS

Table 1 summarizes the characteristics of the 39,400 patients with CHA₂DS₂-VASc scores of 0 to 1 included in the current analysis; 23,572 were not treated after discharge, 5,353 were initiated on aspirin, and 10,475 were initiated on warfarin. The mean follow-up duration was 5.9 years. Approximately 50% of patients with 1 risk factor had age as the only risk factor (>65 years), and 90% had either age or hypertension as the risk factor. Anticoagulated patients with no risk factors were older, with a lower proportion of female subjects. Use of angiotensin receptor blockers or angiotensin-converting enzyme inhibitors and beta-blockers was higher among patients with initiated treatment as well as among those with 1 risk factor.

Rates of stroke, bleeding, and death in relation to no treatment, aspirin, or warfarin use among patients with AF with CHA₂DS₂-VASc scores of 0 to 1 are shown in **Table 2**. Stroke event rates for untreated low-risk patients with a CHA₂DS₂-VASc score of 0 (male) or 1 (female) were 0.49 per 100 person-years at 1 year and 0.47 per 100 person-years at full follow-up on the basis of the ITT analysis. Using a CT approach, corresponding figures were 0.37 and 0.33, respectively.

With 1 additional stroke risk factor, event rates at 1 year for stroke were 1.55 and 1.46 per 100 person-years on ITT and CT. The overall stroke rate among included untreated patients was 0.90 per 100 person-years at 1 year. The 1-year follow-up stroke rate for each calendar year cohort of untreated patients (**Central Illustration**) displayed no marked trends in stroke rate levels from 1998 to 2015.

One-year ischemic stroke rates were 1.39 per 100 person-years among untreated patients and 0.94 among warfarin-treated patients with 1 risk factor (CT). The stroke rates varied with the different risk factors, ranging from 1.13 per 100 person-years for patients with hypertension, 1.40 for heart failure, 1.80 with age 65 to 74 years, and 3.03 for vascular disease (full details not shown). Restricting the analysis to primary diagnoses, the 1-year stroke rates were 0.27 per 100 person-years for low-risk patients and 1.18 per 100 person-years for patients with 1 additional risk factor (CT) (**Online Table 3**).

Bleeding event rates among untreated low-risk patients (CHA₂DS₂-VASc scores of 0 [male] or 1 [female]) were low (1.08 per 100 person-years at 1 year and 0.97 at full follow-up with an ITT approach). For patients who initiated warfarin treatment, the

TABLE 2 Event Rates Per 100 PYs at 1 Year and Full Follow-Up According to Treatment Strategy Initiated at Day 14 After Discharge With Incident AF

	1-Year Follow-Up						Full Follow-Up					
	No Treatment		Aspirin Initiated		Warfarin Initiated		No Treatment		Aspirin Initiated		Warfarin Initiated	
	Events/PY	Rate	Events/PY	Rate	Events/PY	Rate	Events/PY	Rate	Events/PY	Rate	Events/PY	Rate
No risk factors												
ITT												
Stroke	65/13,370	0.49	16/2,048	0.78	27/3,078	0.88	439/9,3572	0.47	88/12,439	0.71	145/18,971	0.76
Ischemic stroke	58/13,372	0.43	16/2,048	0.78	23/3,080	0.75	405/93,683	0.43	84/12,443	0.68	132/18,997	0.69
Bleeding	144/13,329	1.08	31/2,038	1.52	51/3,067	1.66	885/91,568	0.97	157/12,158	1.29	261/18,418	1.42
ICH	20/13,387	0.15	2/2,053	0.10	5/3,093	0.16	81/95,014	0.09	8/12,704	0.06	25/19,466	0.13
Death	519/13,401	3.87	64/2,054	3.12	68/3,093	2.20	1586/95,311	1.66	223/12,731	1.75	364/19,522	1.86
CT												
Stroke	44/12,003	0.37	14/1,897	0.74	24/2,799	0.86	230/69,531	0.33	69/10,296	0.67	88/13,990	0.63
Ischemic stroke	41/12,004	0.34	14/1,897	0.74	20/2,800	0.71	206/69,563	0.30	67/10,297	0.65	80/13,997	0.57
Bleeding	118/11,958	0.99	27/1,886	1.43	47/2,784	1.69	509/67,962	0.75	113/10,003	1.13	174/13,487	1.29
ICH	15/12,005	0.12	2/1,899	0.11	4/2,807	0.14	38/69,652	0.05	6/10,371	0.06	17/14,126	0.12
Death	464/12,017	3.86	60/1,900	3.16	53/2,807	1.89	1009/69,766	1.45	177/10,381	1.71	207/14,142	1.46
1 risk factor*												
ITT												
Stroke	133/8,571	1.55	43/2,964	1.45	55/5,172	1.06	653/52,619	1.24	213/17,416	1.22	334/30,874	1.08
Ischemic stroke	129/8,573	1.50	43/2,964	1.45	53/5,173	1.02	620/52,731	1.18	207/17,421	1.19	316/30,917	1.02
Bleeding	233/8,516	2.74	68/2,949	2.31	124/5,130	2.42	1012/51,452	1.97	373/16,903	2.21	685/29,506	2.32
ICH	31/8,611	0.36	6/2,981	0.20	23/5,189	0.44	132/54,674	0.24	41/18,058	0.23	83/31,897	0.26
Death	978/8,630	11.3	169/2,984	5.66	208/5,197	4.00	3,024/54,979	5.50	752/18,140	4.15	1331/32,107	4.15
CT												
Stroke	98/6,698	1.46	39/2,617	1.49	46/4,664	0.99	317/27,376	1.16	160/12,993	1.23	212/22,271	0.95
Ischemic stroke	93/6,699	1.39	39/2,617	1.49	44/4,665	0.94	297/27,402	1.08	156/12,996	1.20	201/22,298	0.90
Bleeding	177/6,644	2.66	55/2,601	2.11	112/4,626	2.42	401/26,611	1.51	219/12,572	1.74	466/21,244	2.19
ICH	24/6,707	0.36	5/2,625	0.19	22/4,674	0.47	49/27,509	0.18	22/13,183	0.17	67/22,606	0.30
Death	820/6,720	12.2	158/2,627	6.02	175/4,681	3.74	1606/27,619	5.81	527/13,231	3.98	765/22,730	3.37

Stroke rates restricted to primary diagnoses are given in [Online Table w3](#). *Presence of 1 risk factor of age >65 years, CHF/LVD, hypertension, diabetes, or vascular disease.
ICH = intracranial hemorrhage; PY = person-years; other abbreviations as in [Table 1](#).

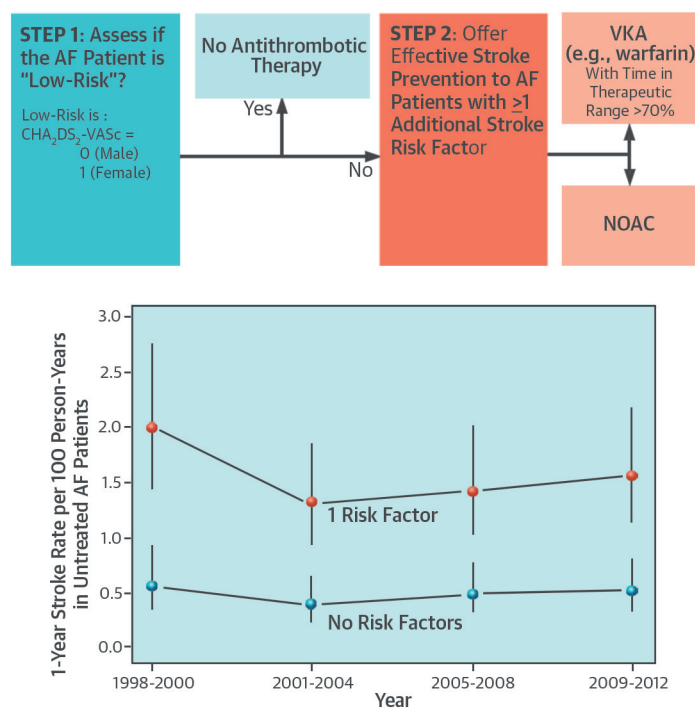
corresponding rates were 1.66 and 1.42 ([Table 2](#)). With additional risk factors, there was a corresponding increase in event rates, with rates at 1 year of 2.42 and at full follow-up of 2.32 for warfarin-treated patients. Similar trends were seen with a CT approach. One-year intracranial hemorrhage event rates among patients with 1 risk factor were ~0.4 for untreated patients and slightly higher for warfarin-treated patients. Death rates with no risk factors for untreated patients were ~3.9 and were much higher for the group of older patients in the group with 1 risk factor.

[Figure 2](#) shows the relative impacts on stroke, bleeding, and death in relation to no treatment, aspirin, or warfarin use according to the presence of 1 stroke risk factor among patients with AF with CHA₂DS₂-VASc scores of 0 to 1, adjusted for potential confounding (exact numbers from the crude and adjusted analyses are presented in [Online Table 4](#)). The presence of 1 stroke risk factor was associated with increased stroke by 3.01-fold, bleeding by 2.35-fold, and death by 3.12-fold (ITT) at 1-year follow-up for patients receiving no treatment. Corresponding

hazard ratios (HRs) for aspirin-treated patients (ITT) were 1.85, 1.62, and 2.09; for warfarin-treated patients, corresponding HRs were 1.25, 1.27, and 2.04, respectively. All increases were significant, except for stroke and bleeding among warfarin-treated patients. HRs in relation to 1 stroke risk factor for stroke, primary diagnoses, ischemic stroke endpoints, and intracranial hemorrhage are given in [Online Table 4](#).

COMPARING THE IMPACT OF ANTITHROMBOTIC TREATMENTS. [Figure 3](#) summarizes HRs comparing aspirin versus no treatment, warfarin versus no treatment, and warfarin versus aspirin, adjusted for potential confounders (exact numbers from the crude and adjusted analyses are presented in [Online Tables 5 and 6](#)). In patients with no risk factors (i.e., low risk with CHA₂DS₂-VASc = 0 [male], = 1 [female]), the adjusted analyses, both at 1 year and at full follow-up, show a neutral or negative association of treatment on stroke, bleeding, or death.

In patients with 1 risk factor (i.e., CHA₂DS₂-VASc = 1 [male], = 2 [female]), there was a trend for a reduction in stroke by warfarin at 1 year (HR 0.76) and

CENTRAL ILLUSTRATION AF and 0 or 1 Additional Stroke Risk Factors

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(Top) Flow chart for assessment and selection of stroke prevention therapy for patients with atrial fibrillation (AF). **(Bottom)** Time trends of 1-year stroke rates per 100 person-years for patients with untreated AF and 0 or 1 stroke risk factors. CHA₂DS₂-VASc = congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischemic attack, vascular disease, age 65 to 74 years, sex category; NOAC = non-vitamin K antagonist oral anticoagulant; VKA = vitamin K antagonist.

neutral for full follow-up (HR: 0.94), but a significant reduction in death (HR: 0.42 and 0.86, respectively). Warfarin was neutral on bleeding at 1 year (HR: 0.97), but there was a significantly higher risk at full follow-up (HR: 1.22 with ITT, 1.62; CT) (Figure 3, Online Tables 5 and 6).

Aspirin did not confer any reduction in stroke versus no treatment (HR: 1.01) at 1 year and at full follow-up (HR: 1.09). At full follow-up, a significant increase in bleeding (HR 1.18 with ITT, 1.31 with CT) was seen for patients with 1 risk factor (Figure 3).

When comparing warfarin versus aspirin, a non-significant reduction in stroke (HR: 0.75) and a significantly lower death rate (HR: 0.68) were seen at 1 year, whereas bleeding rates were slightly increased (HR: 1.06). The CT analysis slightly increased these differences. The CT analysis indicated an increase in bleeding at full follow-up with warfarin versus aspirin (HR: 1.23).

Detailed adjusted analysis of the stroke endpoints in Online Table 5 shows a nonsignificant 1-year reduction in ischemic stroke (HR: 0.74 with ITT, 0.75 with CT), and no significant increase in intracranial hemorrhage (HR: 1.41) (Online Table 6), although rates were low. With CT, bleeding was significantly increased with aspirin and warfarin compared with no treatment at full follow-up.

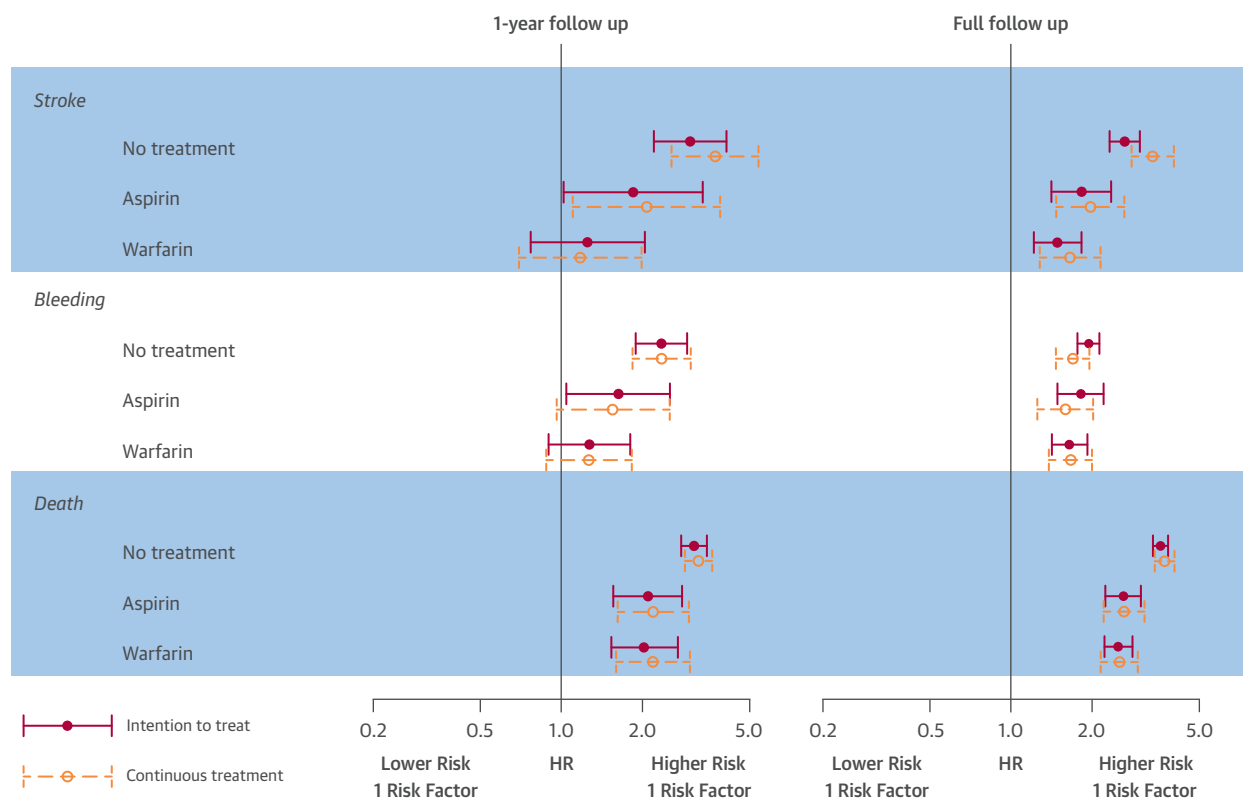
DISCUSSION

In this analysis of a large cohort of patients with CHA₂DS₂-VASc scores of 0 to 1, we show that those defined as low-risk (i.e., CHA₂DS₂-VASc = 0 [male], = 1 [female]) have a truly low risk for stroke, bleeding, and death. In addition, untreated AF patients with 1 additional stroke risk factor (i.e., CHA₂DS₂-VASc = 1 [male], = 2 [female]) are at increased 1-year stroke risk by 3.01-fold, bleeding by 2.35-fold, and death by 3.12-fold. Furthermore, in the patients with 1 risk factor, there were reductions in stroke and death with warfarin versus no treatment and with warfarin versus aspirin, but there was no increase in bleeding with warfarin versus aspirin. Sample size and low rates among treated groups led to some confidence intervals crossing neutral, as with stroke.

These data provide support for the approach advocated in the stroke prevention guidelines from the ESC and NICE, whereby the first decision step is to identify truly low-risk patients (CHA₂DS₂-VASc score = 0 [male], = 1 [female]) who have such low event rates that no antithrombotic therapy is recommended. Indeed, such patients do not have a positive net clinical benefit (NCB) (12) from treatment, suggesting that antithrombotic therapy confers no advantage and, given the negative NCB, a possible disadvantage is evident. Our "real-world" data are also consistent with a modeling analysis by Banerjee et al. (13), in which NOACs had a positive NCB in AF patients with ≥1 stroke risk factor. In large "real-world" cohorts, aspirin did not decrease stroke risk and demonstrated no positive NCB when balancing stroke against serious bleeding (14,15).

Subsequent to the initial step of identifying low-risk patients, effective stroke prevention (i.e., oral anticoagulation) is recommended for patients with ≥1 additional stroke risk factor (CHA₂DS₂-VASc scores ≥1 [male] and ≥2 [female]). Our data support this recommendation, given stroke event rates >1.5 per 100 person-years at 1 year favoring warfarin treatment. Of note, aspirin resulted in a counterintuitive reduction in intracranial hemorrhage rates, perhaps explained by patient selection. Oral anticoagulation is effective stroke prevention, whether delivered as a

FIGURE 2 Plot of Adjusted HR for Outcome in the Presence of 1 Risk Factor of Age >65 Years, Heart Failure (or Left Ventricular Dysfunction), Hypertension, Diabetes, or Vascular Disease



Adjusted for year of diagnosis (categorical), sex, abnormal renal function, abnormal hepatic function, angiotensin receptor blocker or angiotensin-converting enzyme inhibitor use, beta-blocker use, nonsteroidal anti-inflammatory drug use, previous electrical cardioversion, and ablation. HR = hazard ratio.

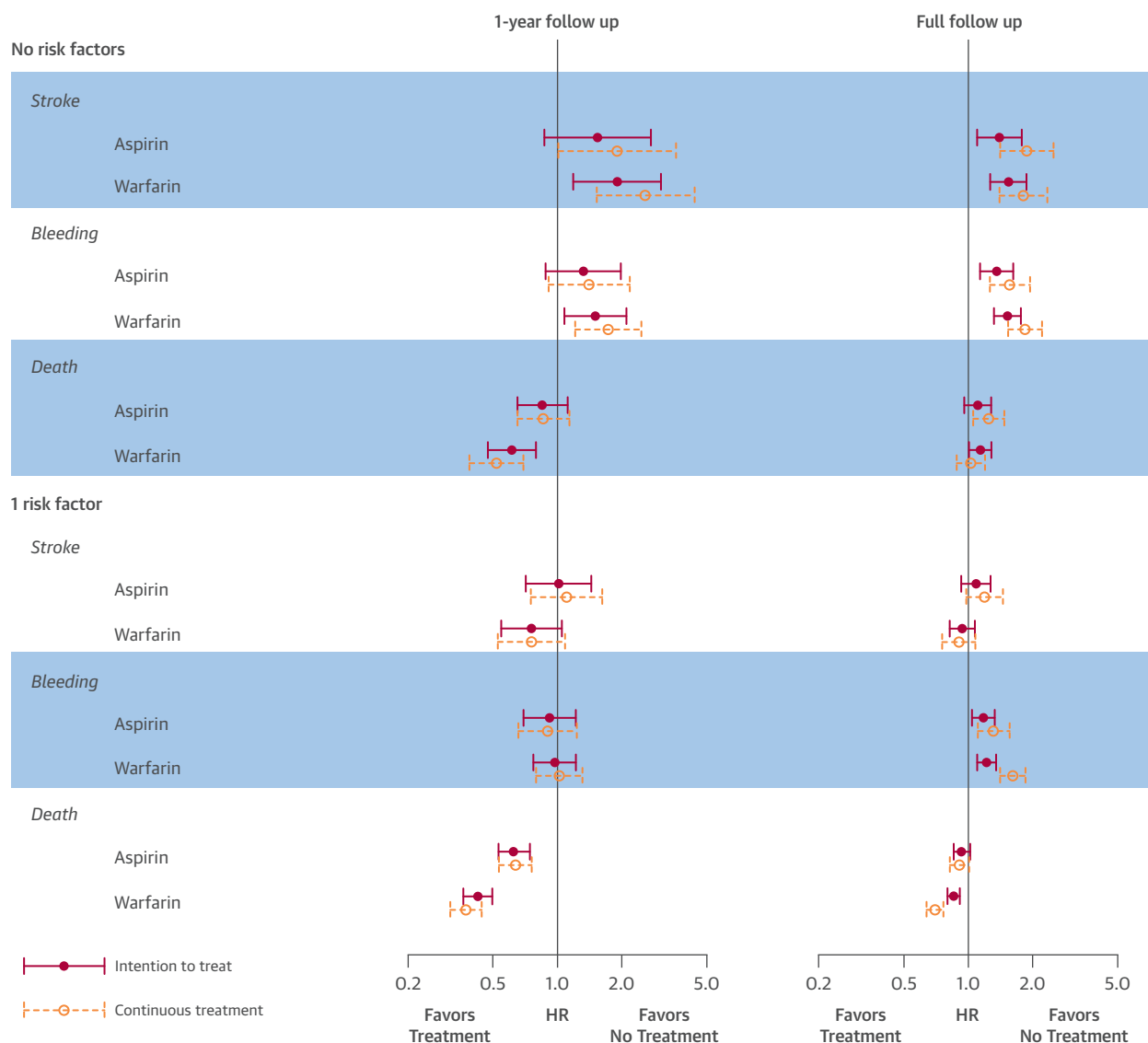
NOAC or good-quality anticoagulation international normalized ratio control with a VKA (time-in-therapeutic range >70%), which offers the best efficacy and safety when VKAs are used (4,5). Indeed, given the availability of NOACs, the threshold for treatment may be a stroke rate of 0.9% per year (16).

It has previously been shown that stroke rates could be as high as 8.1% among patients with a single risk factor (using the older CHADS₂ score [congestive heart failure, hypertension, age ≥75 years, diabetes mellitus [1 point for presence of each], and stroke/transient ischemic attack [2 points] of 1) when substratified according to CHA₂DS₂-VASc score (17). Even among those with a low-risk CHADS₂ score of 0, stroke rates, when substratified according to CHA₂DS₂-VASc scores, can range between 0.8% and 3.2% per year if left untreated. Indeed, when balancing stroke reduction against the potential for serious bleeding, a positive NCB for anticoagulation in AF patients with 1 stroke risk factor has been shown (15). The NICE guidelines clearly recommend that “aspirin

monotherapy should not be offered for stroke prevention in AF patients,” whereas oral anticoagulation should be offered to those with a CHA₂DS₂-VASc score ≥2 and offered to men with a CHA₂DS₂-VASc score of 1. This recommendation, therefore, is in alignment with the 2012 ESC guidelines (7).

Although the 2014 American Heart Association/American College of Cardiology/Heart Rhythm Society guidelines recommend oral anticoagulation for a CHA₂DS₂-VASc score ≥2, the recommendations for a CHA₂DS₂-VASc score of 1 state “no therapy, aspirin or anticoagulation” (9). Female patients with a CHA₂DS₂-VASc score of 1 (by virtue of their sex) are low risk (hence, no antithrombotic therapy is necessary), but male patients with a CHA₂DS₂-VASc score of 1 would be left without stroke prevention if “no therapy or aspirin” were offered and would be at risk of fatal and disabling strokes. In a recent study of untreated AF patients with CHA₂DS₂-VASc scores of 1, the annual incidence of stroke was 6.6%, with the greatest risk conferred by hypertension and

FIGURE 3 Plot of Adjusted HR for Outcome According to Treatment Versus No Treatment Within Strata of the Presence of 1 Risk Factor of Age >65 Years, Heart Failure (or Left Ventricular Dysfunction), Hypertension, Diabetes, or Vascular Disease



Adjusted for year of diagnosis (categorical), sex, abnormal renal function, abnormal hepatic function, angiotensin receptor blocker or angiotensin-converting enzyme inhibitor use, beta-blocker use, nonsteroidal anti-inflammatory drug use, previous electrical cardioversion, and ablation. HR = hazard ratio.

age 65 to 74 years (10). Even among patients unsuited for warfarin treatment, in whom the common practice previously was to offer aspirin, the oral factor Xa inhibitor apixaban was superior to aspirin for stroke prevention, with a similar rate of major bleeding and intracranial hemorrhage (18). Of note, other guidelines (19,20), including the previous U.S. guidelines (21), recommended oral anticoagulation to patients with 1 stroke risk factor (on the basis of the older CHADS₂ score [22]), and both CHA₂DS₂-VASc and CHADS₂

scores have many stroke risk factors in common. In essence, some risk factors weighted at 1 in the CHA₂DS₂-VASc score have the same score value in the older CHADS₂ score, in which even the older guidelines recommend oral anticoagulation. Otherwise, such patients (even with a single stroke risk factor) will be exposed to unnecessary risk of disabling or even fatal thromboembolic complications or death (10,23) that could otherwise have been prevented. Patients with AF are desperate to avoid strokes, and a recent

survey on patients' values and preferences showed that patients were prepared to accept with oral anticoagulation 4.4 episodes of major bleeding just to prevent 1 stroke (24). In randomized trials, oral anticoagulation significantly reduces stroke and all-cause mortality, compared with use of control/placebo (1), and similar trends were seen in the current study for patients with ≥ 1 additional stroke risk factor.

STUDY LIMITATIONS. We acknowledge the limitations of our observational cohort design, as with similar “real-world” cohort data. In Danish registries, the positive predictive value of the AF diagnosis is high (97%) (25), although our hospitalized patients with AF may have been a higher risk group for stroke and bleeding, and the applicability to community-based (and often asymptomatic and “uncomplicated”) AF cohorts is less uncertain. Our event rates probably differ from other published cohorts, given the dependence on definitions used for the particular dataset and endpoints, as well as populations studied (e.g., community vs. hospitalized), participation in a health care plan (vs. none), and trial (vs. nontrial) cohorts, among others. In addition, the type of AF (paroxysmal, persistent, or permanent) is not captured in Danish registries. Nonetheless, this study included patients with AF diagnosed both in-hospital and at ambulatory visits.

Although patients with AF in the low-risk stratum have a low rate of hospitalization, this finding is neither static nor predictable, and all published data show that hospitalization risks with AF are real (and increasing). Of note, the risk score assignment was made at baseline and was unaffected or not updated thereafter. Thus, during the first year, the CHA₂DS₂-VASc score (and its impact on event rates) was accurately estimated, but as time passed (i.e., for the full follow-up period), it may have become somewhat less accurate.

Some event rates in the nonanticoagulated group may be influenced by use of aspirin bought without a prescription, although the proportion of over-the-counter use is small (26), and it would be unlikely that patients recommended aspirin treatment on a regular basis would buy it in the pharmacy without reimbursement. Given the (nonsignificant) stroke reduction of 19% compared with control/placebo in historical trials, aspirin probably has only a small effect on stroke. The national prescription registry does not provide information on indications for treatment; hence, the aspirin-treated group may especially include patients given aspirin for other indications and perhaps not as a permanent treatment. This potential misclassification could have influenced the estimated rates.

Unmeasured confounding is inevitable in observational studies. Even though the Danish registers provide almost full coverage of history of hospital diagnoses and prescriptions, relevant information from general practice that may potentially explain some effects is still unavailable. Our registry design also does not provide details regarding drug changes over time nor of the quality of anticoagulation control (e.g., time-in-therapeutic range). We recognize that treatment adherence/discontinuation is an important consideration for patient management (27), but a thorough analysis is beyond the scope of this paper, which addresses the question of whether CHA₂DS₂-VASc would be best managed with “nothing, aspirin, or warfarin” on the basis of “real-world” observational data.

CONCLUSIONS

Low-risk patients (i.e., CHA₂DS₂-VASc = 0 [male], = 1 [female]) have a truly low risk for stroke, intracranial bleeding, and major bleeding. With 1 additional stroke risk factor (i.e., CHA₂DS₂-VASc = 1 [male], = 2 [female]), there was a significant increase in event rates, particularly mortality, if nonanticoagulated.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Because estimates of the absolute risk of thromboembolism vary, it is controversial whether male patients with nonvalvular AF who have 1 CHA₂DS₂-VASc risk factor or women with 2 risk factors are at high enough risk of stroke to warrant long-term oral anticoagulant therapy.

COMPETENCY IN PATIENT CARE: For men with AF and a CHA₂DS₂-VASc score of 1 or women with a score of 2, the 2012 ESC guidelines recommend anticoagulation, whereas the 2014 American Heart Association/American College of Cardiology/Heart Rhythm Society guidelines allow the options of oral anticoagulation, aspirin, or no therapy.

TRANSLATIONAL OUTLOOK: Randomized trials of antithrombotic therapy would require very large numbers of patients, but data from inclusive, prospective registries may inform clinical practice.

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APPENDIX For supplemental tables, please see the online version of this article.